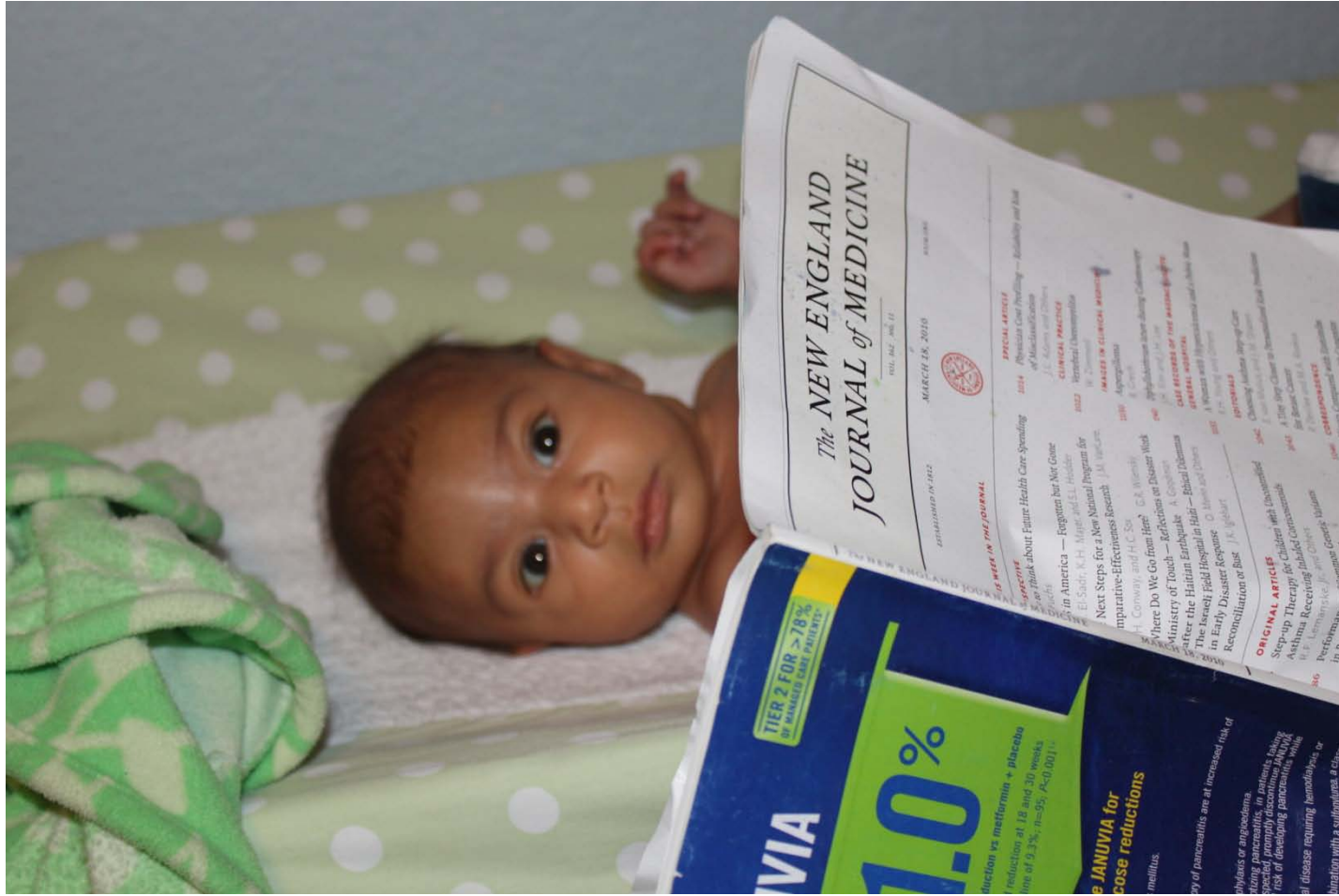


Hypertension: An Update

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CCRMC Noon Conference
October 8, 2010

My research assistant: Thomas



Disclaimers

- This talk is only about medications
- There are few wrong ways to treat HTN

Epidemiology

- Affects > 25% of adults in the developed world
- Affects 65 million adults in the U.S.
 - Only 35% are treated to goal

Why treat?

- Linear relationship between BP and CV risk
 - From 115/75 to 185/115, every
↑ SBP 20 mmHg or ↑ DBP 10 mmHg
doubles risk of fatal coronary event
- Shortens life expectancy by 5 years
- Bigger bang for your buck?

Tight BP control vs. Tight glycemic control

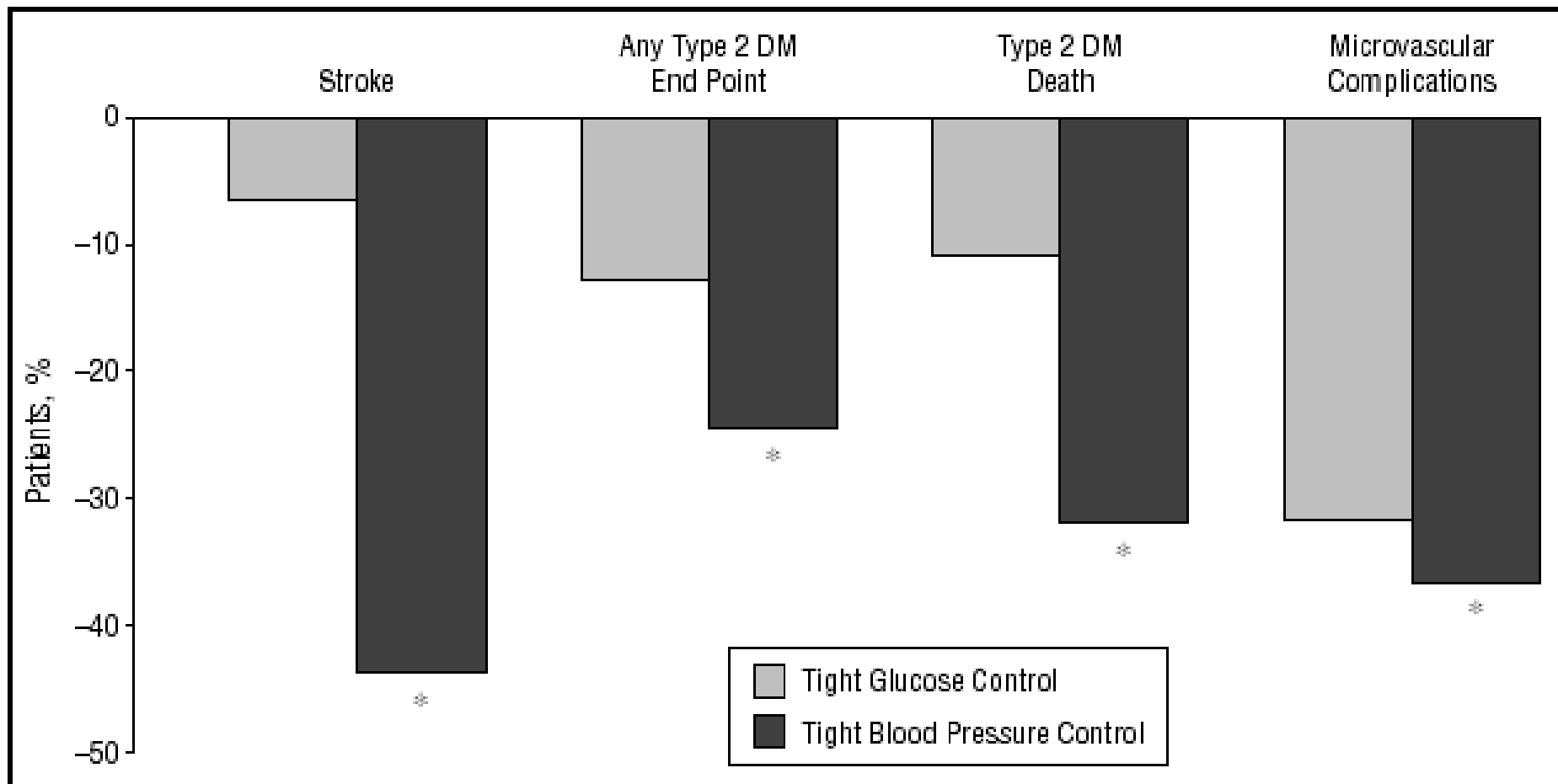


Figure 2. Comparative effects of tight glucose control vs tight blood pressure control in the United Kingdom Prospective Diabetes Study.⁹ Asterisk indicates $P < .05$ compared with glucose control; DM, diabetes mellitus. Reproduced with permission from Bakris et al.³



BP Goals? Depends on who you ask

- JNC7 (2003)
 - CKD or DM: <130/80
 - Everyone else: <140/90
- AHA (2007)
 - CKD, DM, CAD, or CAD risk equivalent, or Framingham 10-year CV risk >10%: <130/80
 - LV systolic dysfunction/CHF: consider <120/80
- NKF (2000)
 - Same as JNC 7 but if CKD with >1 g/d proteinuria: consider <125/75

BP goal in diabetics: Is lower better?

- INVEST trial (Hypertensive CAD pts randomized to verapamil SR- vs. atenolol-based regimens), N=22,576
- Observational data on 6400 INVEST patients with diabetes, divided into 3 groups based on avg SBP during trial:
 - Tight control (<130 mm Hg)
 - Usual control (130–139 mm Hg)
 - Uncontrolled (>139 mm Hg)
- At 3 years, all-cause mortality or nonfatal MI or stroke:
 - Tight control: 12.7%
 - Usual Control: 12.6%
 - Uncontrolled: 19.8%



BP goal in diabetics: Is lower better?

- ACCORD Blood Pressure Trial
 - N = 4,773 diabetics, mean age 62, mean A1C 8.3, mean BP 139/76, third with h/o CV event
 - intensive BP control (target SBP <120 mmHg) vs. standard BP control (target SBP <140 mmHg)
 - Results:
 - At 1 year, Avg SBP 119 vs. 134 (3.4 meds vs. 2.1 meds)
 - At 5 years, CV event rate 1.9% vs 2.1% (HR 0.88, $P=0.2$)
 - Adverse events due to meds: 3.3% vs. 1.3% ($P<0.001$)

BP goal in diabetics: Is lower better?

- ACCORD and INVEST suggest that goal SBP < 140 is reasonable for patients with diabetes, despite JNC7 recommendation.
- JNC8 guidelines due in 2011.

BP goal in CKD: Is lower better?

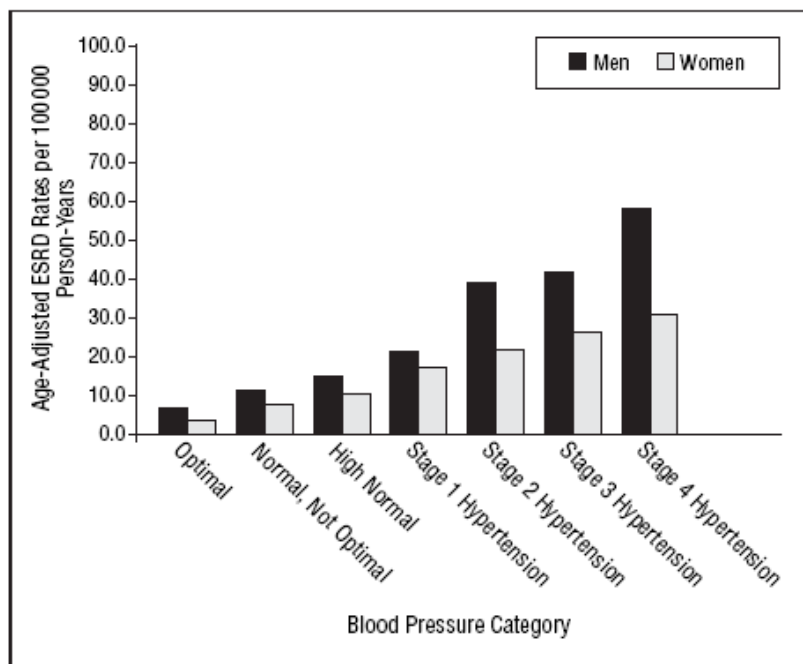


Figure 1. Age-adjusted risk for end-stage renal disease (ESRD) in subgroups stratified by sex according to Fifth Joint National Committee Report,²² blood pressure category.

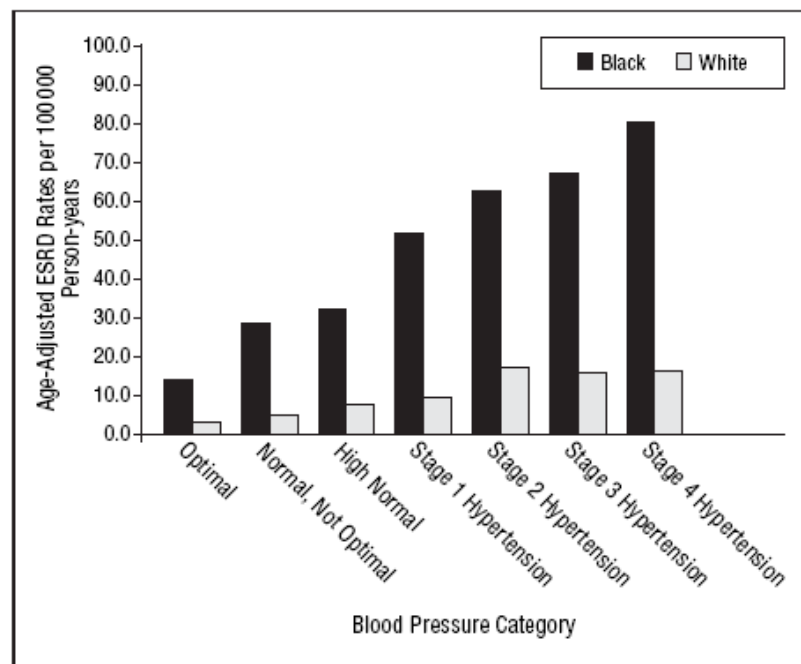


Figure 2. Age-adjusted risk for end-stage renal disease (ESRD) in subgroups stratified by race according to Fifth Joint National Committee Report,²² blood pressure category.

Hsu et al. Elevated Blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med. 2005;165:923-928

BP goal in CKD: Is lower better?

- AASK Study: Intensive BP control in AA patients with hypertensive CKD
- Trial phase followed by Cohort phase (roughly 5 years each)
- N = 1094
- Trial phase
 - Intensive group: Goal MAP <92 (<130/80)
 - Standard group: Goal MAP 102-107 (<140/90)
- Cohort Phase: Goal BP <130/80 both groups

BP goal in CKD: Is lower better?

- AASK Study (cont'd)
- Results:
 - Mean BP achieved during trial phase
 - Intensive group: 130/78
 - Standard group: 141/86
 - Mean BP achieved during cohort phase
 - Intensive group: 131/78
 - Standard group: 134/78

BP Goal in CKD: Is lower better?

- AASK Study (cont'd)
- Primary outcome: Progression of CKD (doubling of Cr, dx ESRD, or death)
- In both phases, no difference in outcome
- However, subgroup with proteinuria (defined as >300 mg/day) showed benefit with intensive BP control
 - Trial phase: HR 0.74, P=0.04
 - Cohort phase: HR 0.66, P=0.07
 - Both phases: HR 0.73, P=0.01

BP goals in diabetes & nonproteinuric CKD

- My take home points:
 - Goal SBP < 130 is based primarily on observational data
 - If you achieve SBP < 140, pat yourself (and your patient) on the back. Consider going lower (< 130), but don't kill yourself (or your patient) trying to get there.



What about the very elderly?

- HYVET trial
 - N = 3,845 patients age ≥ 80 with SBP ≥ 160 mmHg (Mean age 83.6, 12% w/CVD, mean BP 173/91)
 - Treatment group: indapamide \pm perindopril for goal SBP $\leq 150/80$ vs. placebo
 - Results: At 2 years,
 - Mean BP lower by 15/6
 - Stroke \downarrow 30%, Death stroke \downarrow 39%
 - All-cause mortality \downarrow 21%
 - Heart failure \downarrow 64%
 - Serious adverse events: fewer in tx group ($P < 0.001$)

What about the very elderly?

- Notable exclusion criteria:
 - Hemorrhagic stroke in last 6 months
 - Heart failure requiring tx with antihypertensive
 - Serum Cr > 1.7; Serum K < 3.5 or > 5.5
 - Gout
 - Dementia
 - Requires nursing care
- My take home
 - It appears beneficial and safe to treat robust patients age ≥ 80 to a goal BP $\leq 150/80$.
 - What if they are not “robust”? No trial data. Extrapolate judiciously.

What drugs should we use?

What drugs should we use?

- Now I'll delve into the details about individual drugs, but remember...
- How you reach your BP goal is not nearly as important as getting there!

Thiazide diuretics

- **Chlorthalidone** is the preferred thiazide diuretic because:
 - Chlorthalidone was the agent used in the largest hypertension clinical trials with patient-oriented outcomes (eg, ALLHAT).
 - Chlorthalidone is 1.5 to 2 times as potent as HCTZ at the same dose (Ernst 2006)
 - Chlorthalidone has a longer half-life (45-60 hrs vs. 8-15 hrs for HCTZ) (Khosla 2005)

Thiazide diuretics

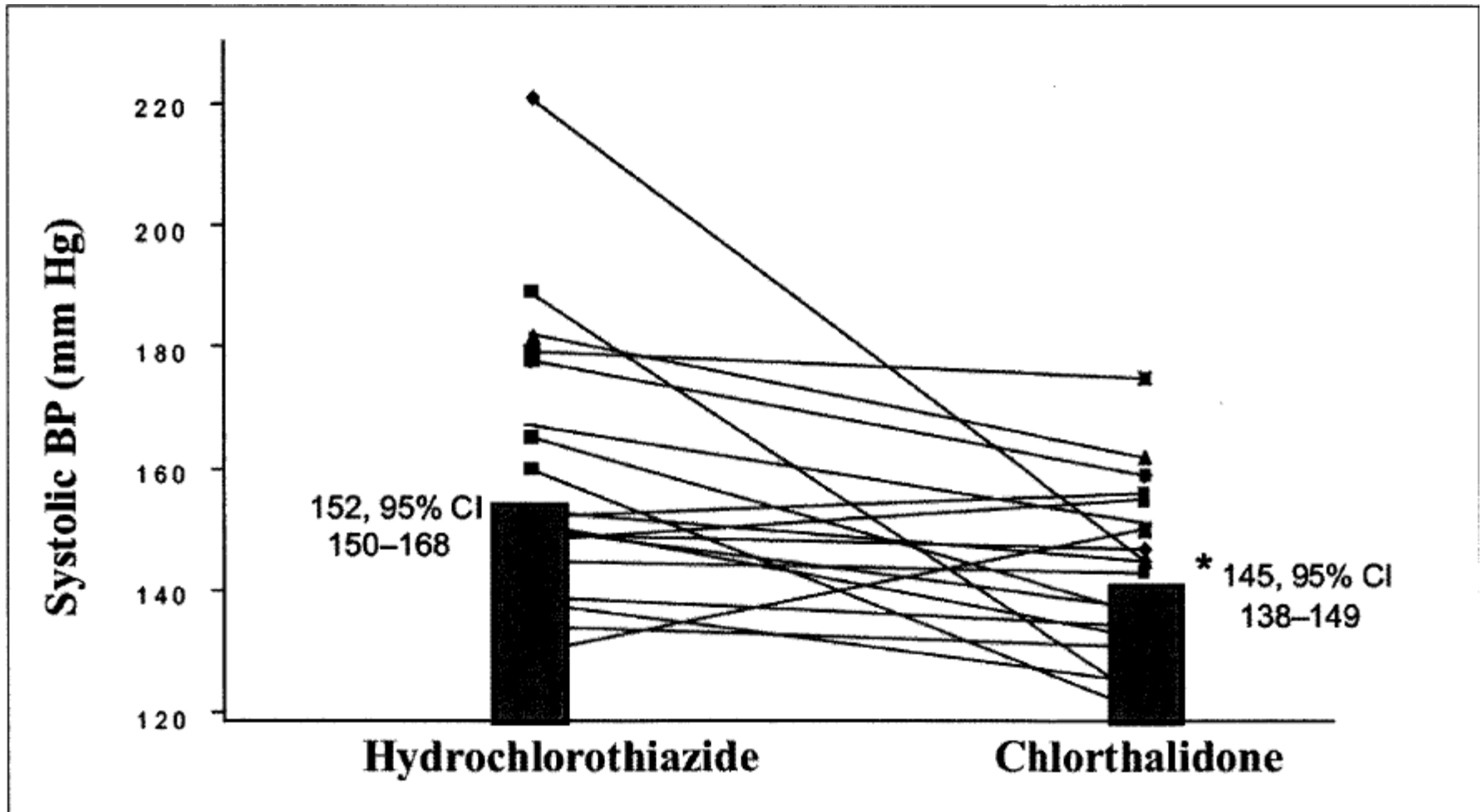
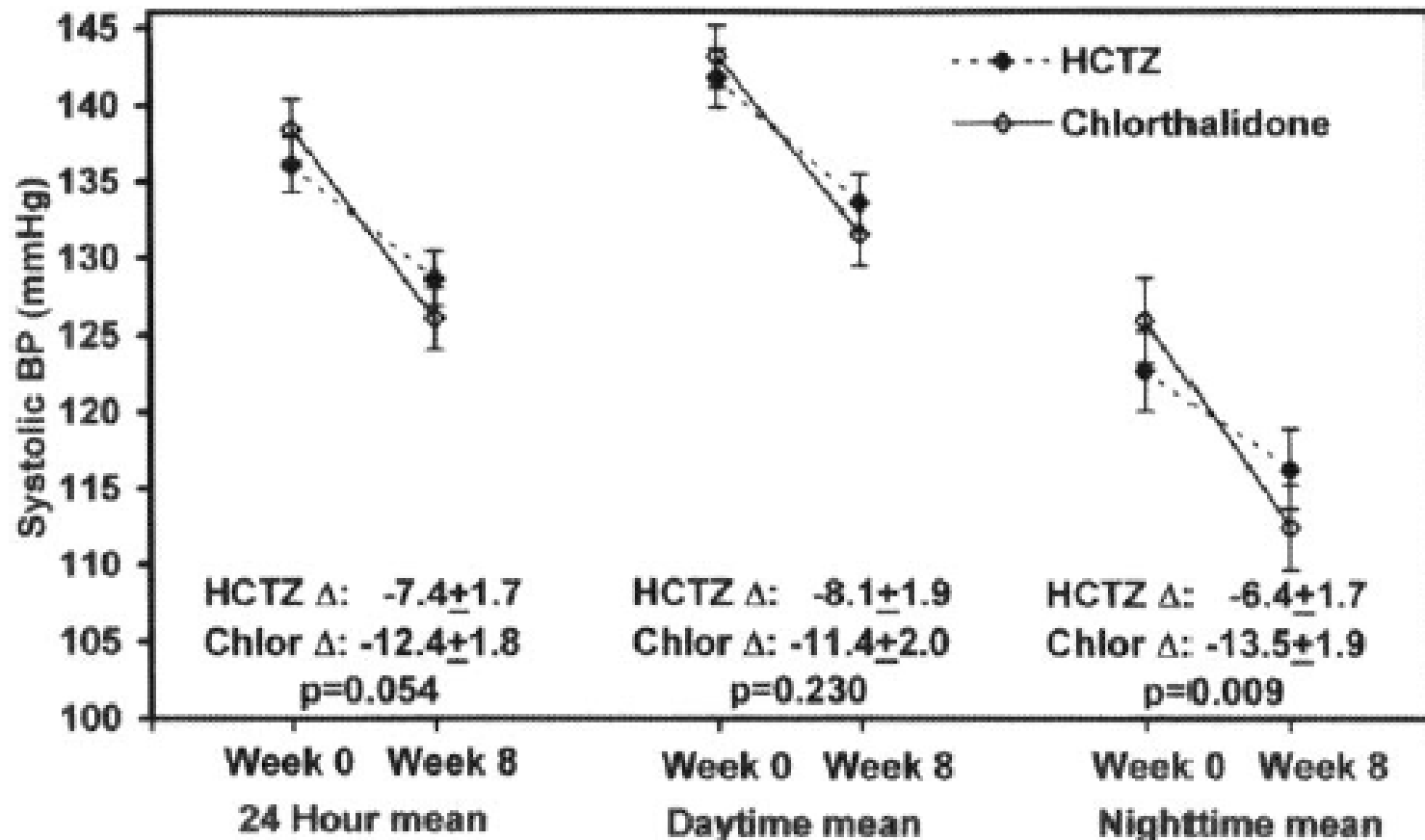


Figure. Changes in median systolic blood pressure (BP) after 6–8 weeks in each of 19 patients on stable doses of hydrochlorothiazide who were changed to the same dose of chlorthalidone. CI=confidence interval; *p=0.035. Shaded boxes represent median value for each group.

Khosla 2005: 17 of 19 patients were taking 25 mg HCTZ → chlorthalidone, other two 12.5 mg. Excluding the 2 patients with greatest benefit reduced mean difference from 7 to 4 mmHg SBP.

Thiazide diuretics



Ernst 2006: Randomized crossover trial (n=30) comparing HCTZ 50 mg vs chlorthalidone 25 mg. Data shown are from 24-hour ambulatory blood pressure monitoring (ABPM). ABPM correlates more closely with CV outcomes than office BP.

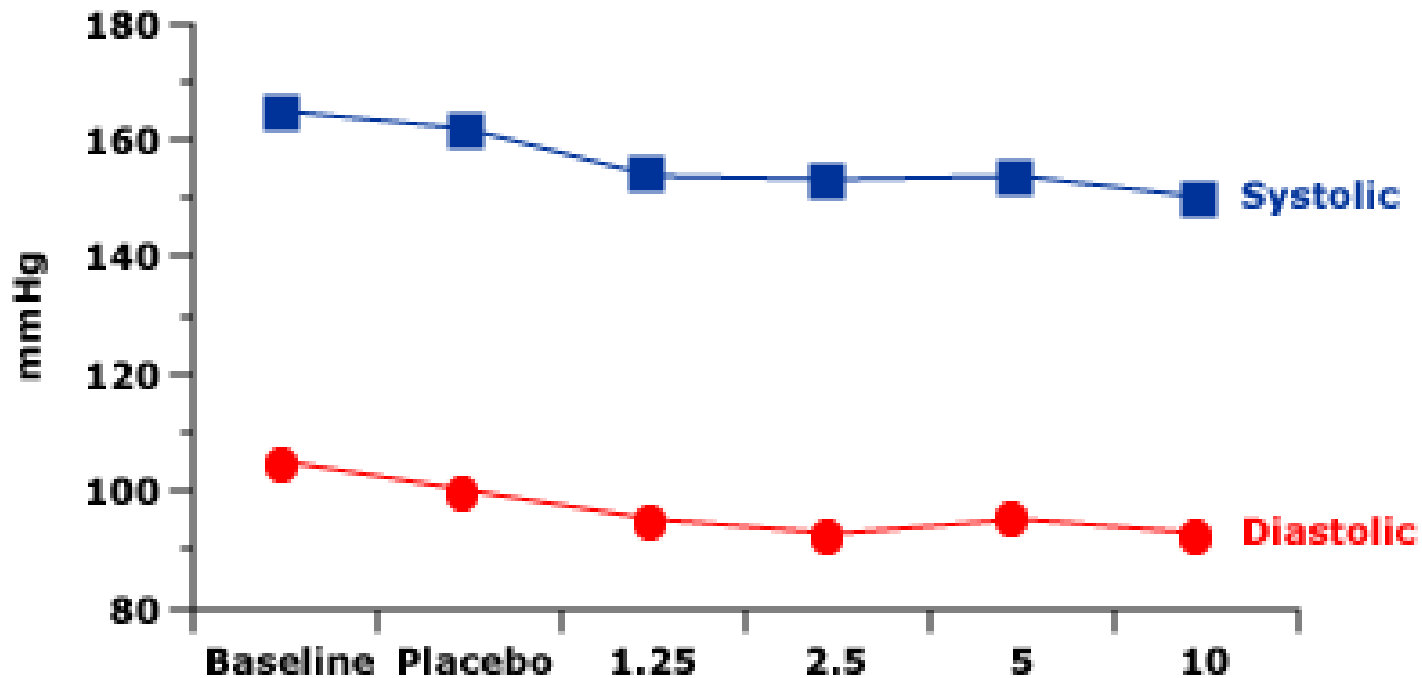
Thiazide diuretics

- The primary advantage HCTZ has over chlorthalidone is its availability in combination pills with several other classes of antihypertensive drugs (eg, HCTZ/lisinopril).
- Consider using HCTZ instead of chlorthalidone when patient adherence or out-of-pocket expense would benefit from combination pills.

Thiazide diuretics

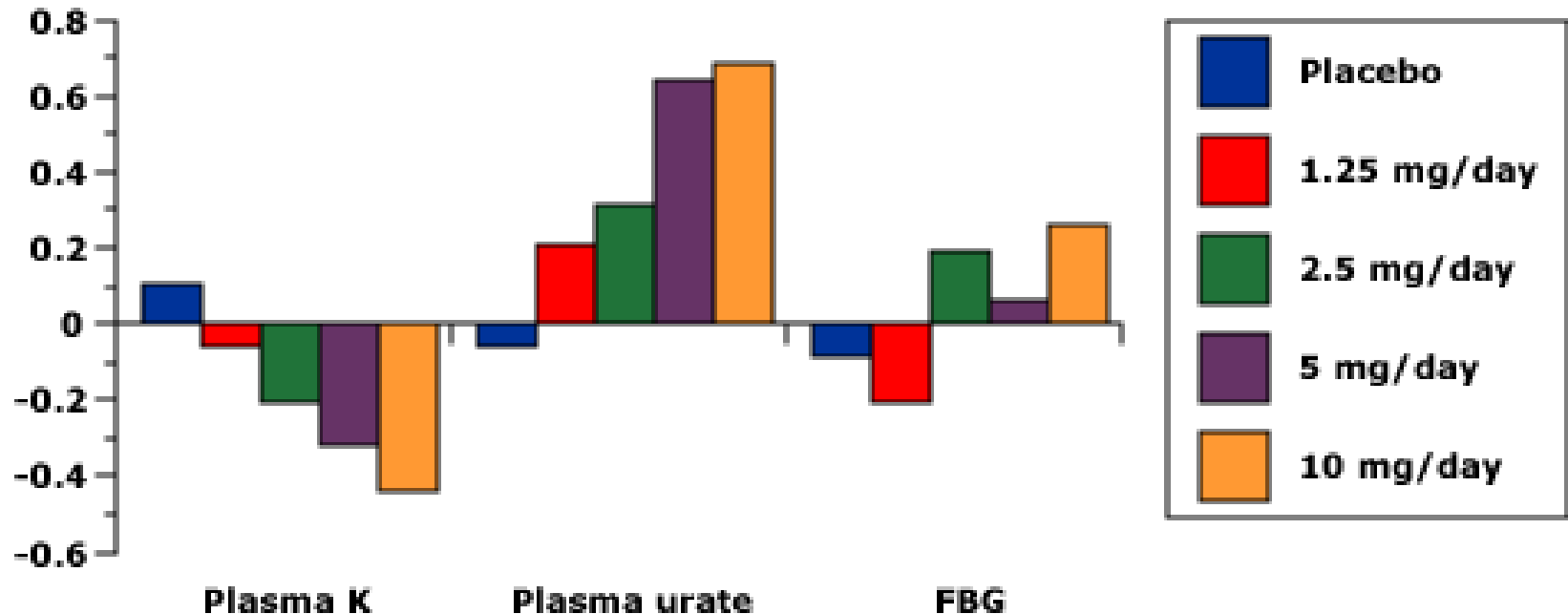
- Thiazides may outperform other drugs in BP reduction when used in combination therapy
 - VA Single Drug Therapy Cooperative Study: patients not controlled (DBP >90) on one randomly assigned antihypertensive medication (thiazide diuretic, ACE inhibitor, BB, CCB, alpha-blocker, or a centrally acting alpha agonist) were then randomized to one of the other medications. If DBP was still not controlled, the first medication was added back to test the various 2-drug combinations: the combinations that included a diuretic were consistently more effective than combinations that did not include a diuretic (n=102, Materson 1995)

Thiazide diuretics: Does dose matter?



Antihypertensive response to bendrofluazide in relation to daily dose (in mg, multiply by 10 to get approximate equivalent doses of hydrochlorothiazide). The initial dose of 1.25 mg/day lowers the blood pressure in comparison to placebo; however, higher doses produced little further antihypertensive response. Each treatment group contained approximately 52 patients. Data from Carlsen, JE, Kober, L, Torp-Pedersen, C, Johannsen, P, BMJ 1990; 300:975.

Thiazide diuretics: Does dose matter?



Metabolic complications induced by bendrofluazide in relation to daily dose (multiply by 10 to get equivalent doses of hydrochlorothiazide). Increasing the dose led to progressive hypokalemia and hyperuricemia and a greater likelihood of a mild elevation in the fasting blood glucose (FBG), all without a further reduction in the systemic blood pressure. Each treatment group contained approximately 52 patients. Data from Carlsen, JE, Kober, L, Torp-Pedersen, C, Johannsen, P, BMJ 1990; 300:975.

Thiazide diuretics: Does dose matter?

- So, in patients with uncomplicated HTN with normal renal function, consider starting with chlorthalidone (or HCTZ) 12.5 mg.
- CKD: If $GFR < 30$, thiazide diuretics are ineffective. Substitute with loop diuretic.
Examples:
 - **furosemide bid** (usual dose range 10 bid – 40 bid)
 - **torseamide qd** (usual dose range 2.5 qd – 10 qd)
(torseamide is on CCHP formulary!)

Beta-blockers: Compelling indications

- **Post-MI**

- resting HR reduction correlated with magnitude of clinical benefit of BB. Each 10 bpm reduction in the HR is estimated to reduce the relative risk of cardiac death by 30% (Cucherat 2007).
- Duration?
 - “Since the large majority of the deaths in the randomized trials occurred during the first year after discharge, there is at present no direct evidence as to the net effects on mortality of continuing beta-blockade beyond the first year or two, although it is reasonable to presume that some risk reduction will continue.” (Yusuf 1985)
 - “Although efficacy of metoprolol tartrate beyond 3 months has not been conclusively established, data from studies with other beta-blockers suggest that treatment should be continued for 1 to 3 years” (Lopressor package insert 2008)

- **LV systolic dysfunction/CHF**

- BB benefit was associated with magnitude of HR reduction, not BB dose . For every HR reduction of 5 bpm, there was an 18% reduction in the risk of death (McAlister 2009).
- Which drugs? Most evidence is for **carvedilol, metoprolol succinate, and bisoprolol**

Beta-blockers: Compelling indications

- Anti-anginal
- Rate-control of SVT (and possible mild antiarrhythmic effect for SVT)
- Suppression of ventricular arrhythmias

Beta-blockers: Fall from grace?

- 2007 **AHA** guidelines and the England's 2006 National Institute for Health and Clinical Excellence (**NICE**) guidelines no longer endorse BBs as 1st-line treatment for uncomplicated HTN
- 2007 European Society of Hypertension/European Society of Cardiology (**ESH/ESC**) HTN guidelines state: *"BBs, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes."*
- So what's left for 1st-line therapy (in no particular order):
 - Thiazide diuretic
 - ACEI/ARB
 - CCB
- Will JNC8 follow suit?

Table 1 Overview of Major Meta-Analyses of Randomized Controlled Trials of Beta-Blockers in Patients With Hypertension

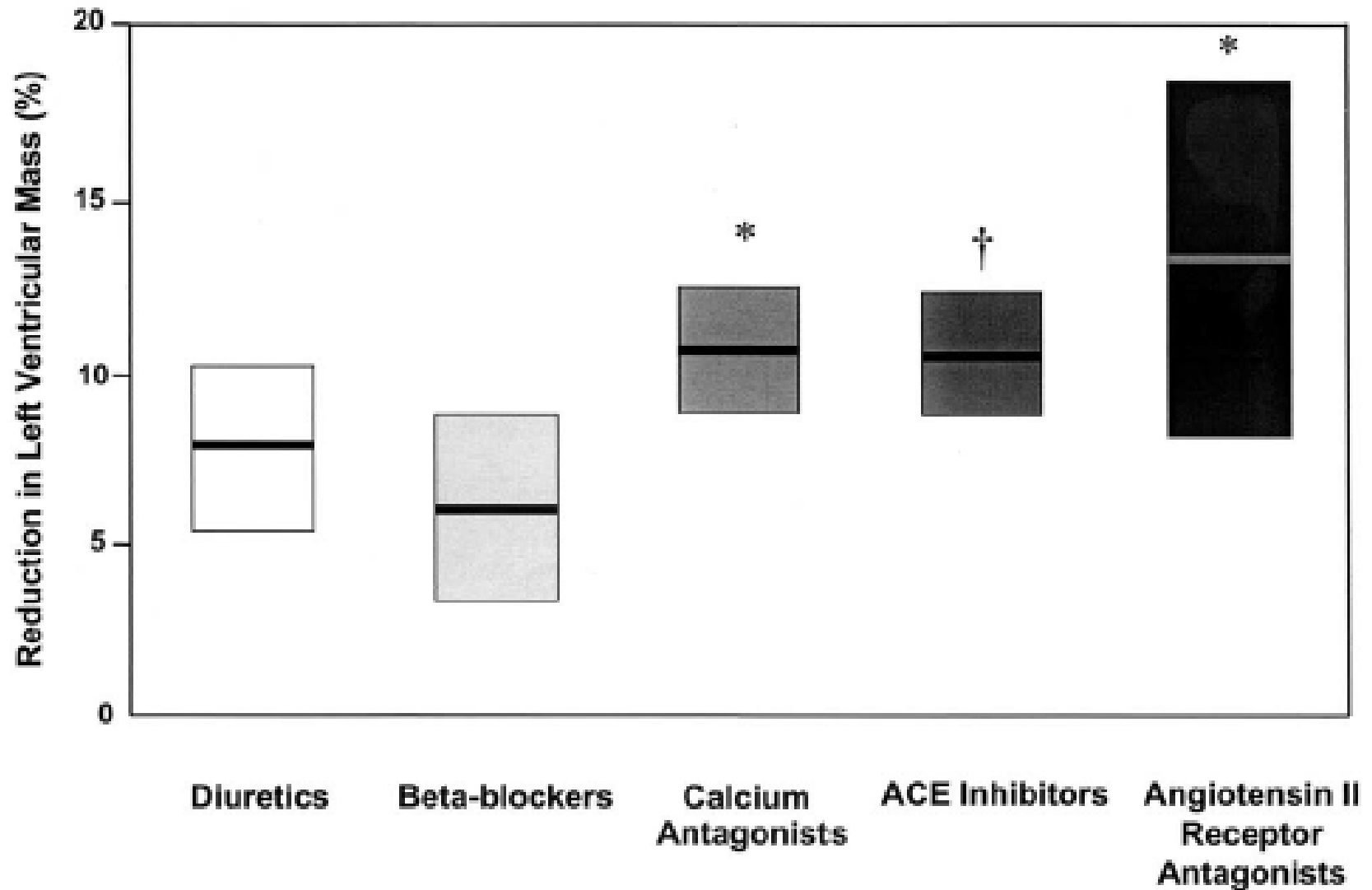
Meta-Analysis	Parameter	No. of Trials	Mortality	Myocardial Infarction	Stroke
vs. placebo					
Cochrane, 2007 (18)	Overall	4	0.99 (0.88–1.11)	0.93 (0.81–1.07)	0.80 (0.66–0.96)
Bradley et al., 2006 (12)	Overall	4	0.99 (0.88–1.11)	0.93 (0.81–1.07)	0.80 (0.66–0.96)
Khan et al., 2006 (14)	Younger	2	0.94 (0.79–1.10)	0.85 (0.71–1.03)	0.84 (0.65–1.10)
Khan et al., 2006 (14)	Elderly	5	0.91 (0.74–1.12)	0.98 (0.83–1.16)	0.78 (0.63–0.98)
Lindholm et al., 2005 (15)	Overall	7	0.95 (0.86–1.04)	0.93 (0.83–1.05)	0.81 (0.71–0.93)
Carlberg et al., 2004 (13) (atenolol)	Overall	4	1.01 (0.89–1.15)	0.99 (0.83–1.19)	0.85 (0.72–1.01)
vs. other antihypertensive agents					
Khan et al., 2006 (14)	Younger	5	0.97 (0.83–1.14)	0.97 (0.86–1.10)	0.99 (0.67–1.44)
Khan et al., 2006 (14)	Elderly	7	1.05 (0.99–1.11)	1.06 (0.94–1.20)	1.18 (1.07–1.30)
Lindholm et al., 2005 (15)	Overall	13	1.03 (0.99–1.08)	1.02 (0.93–1.12)	1.16 (1.04–1.30)
Carlberg et al., 2004 (13) (atenolol)	Overall	5	1.13 (0.97–1.33)	1.04 (0.89–1.20)	1.30 (1.12–1.50)
vs. diuretics					
Cochrane, 2007 (18)	Overall	4	1.04 (0.91–1.19)	1.12 (0.82–1.54)	1.17 (0.65–2.09)
Bradley et al., 2006 (12)	Overall	5	1.04 (0.91–1.19)	1.12 (0.82–1.54)	1.17 (0.65–2.09)
Psaty et al., 2003 (16)	Overall	Network	1.01 (0.93–1.10)	1.15 (0.97–1.35)	1.11 (0.94–1.31)
vs. calcium antagonists					
Cochrane, 2007 (18)	Overall	4	1.07 (1.00–1.14)	1.05 (0.96–1.15)	1.24 (1.11–1.40)
Bradley et al., 2006 (12)	Overall	4	1.07 (1.00–1.14)	1.05 (0.96–1.15)	1.24 (1.11–1.40)
BPLTTC, 2003* (17)	Overall	9	1.01 (0.96–1.05)	0.99 (0.93–1.06)	1.07 (1.00–1.16)
vs. RAAS blockers					
Cochrane, 2007 (18)	Overall	3	1.10 (0.98–1.24)	0.90 (0.76–1.06)	1.30 (1.11–1.53)
Bradley et al., 2006 (12)	Overall	3	1.08 (0.95–1.23)	0.90 (0.76–1.06)	1.30 (1.11–1.53)
BPLTTC, 2003 (17)	Overall	9	1.00 (0.95–1.05)	1.02 (0.95–1.10)	0.92 (0.85–1.00)

Numbers represent hazard ratio (95% confidence interval).

BPLTTC = Blood Pressure Lowering Treatment Trialists' Collaboration; RAAS = renin angiotensin aldosterone system.

Beta-blockers: Fall from grace?

- BP reduction: BB performed worse than other 1st-line agents in some studies (STOP-1, LIFE, ASCOT-BPLA)
- Less effect on central aortic pressure, which may be more important than peripheral pressure
- Effect on LVH regression: outperformed by ACEI/ARB and CCB
- Decreased exercise endurance in healthy patients and those with uncomplicated HTN
- Side effects/compliance: In meta-analyses of RCTs, risk of treatment withdrawal was 80% greater than diuretics and 41% greater than ACEI/ARB (Bradley 2006)
- Hyperglycemia/new-onset diabetes (Elliott 2007, Gress 2000)
- Affect on lipid profile: ↑ TG , ↓ HDL (Kasiske 1995)
- Weight gain: In trials that do report weight changes, BBs are associated with a weight gain of 1.2 kg (range -0.4 to +3.5 kg) (Pischon 2001)
- Hyperkalemia (Traub 1980)



Klingbeil, A., M. Schneider, et al. (2003). "A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension." *Am J Med* 115: 41-46.

TABLE 3. RISK OF DIABETES MELLITUS AMONG 3804 SUBJECTS WITH HYPERTENSION, ACCORDING TO CATEGORY OF ANTIHYPERTENSIVE MEDICATION.*

ANTIHYPERTENSIVE MEDICATION	HAZARD RATIO (95% CONFIDENCE INTERVAL)		
	MODEL 1	MODEL 2	MODEL 3
None	1.0	1.0	1.0
ACE inhibitor	0.99 (0.73–1.35)	0.96 (0.71–1.31)	0.98 (0.72–1.34)
Beta-blocker	1.26 (1.03–1.52)†	1.25 (1.03–1.52)†	1.28 (1.04–1.57)†
Calcium-channel antagonist	1.17 (0.85–1.62)	1.16 (0.84–1.60)	1.17 (0.83–1.66)
Thiazide diuretic	0.95 (0.77–1.17)	0.93 (0.76–1.15)	0.91 (0.73–1.13)

*Model 1 adjusted for age, sex, race, and use of other antihypertensive medications. Model 2 adjusted for the variables included in model 1, as well as body-mass index, waist-to-hip ratio, level of education, smoking status, alcohol use, and physical-activity level. Model 3 adjusted for the variables included in model 2, as well as systolic blood pressure, diastolic blood pressure, fasting serum insulin concentration, and the presence or absence of hypercholesterolemia, cardiovascular disease, pulmonary disease, renal insufficiency, and a family history of diabetes. ACE denotes angiotensin-converting enzyme.

† $P < 0.05$ for the comparison with subjects taking no antihypertensive medication.

Gress, T. W., F. J. Nieto, et al. (2000). "Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus." *NEJM* 342: 905-912.

Table I. *Data in 18 hypertensive patients at the end of each period*

	<i>No treatment</i>	<i>Pindolol</i>	<i>p*</i>	<i>Propranolol</i>	<i>p†</i>
Supine systolic BP (mm Hg)	164.3 ± 4.5‡	155.2 ± 6.2	0.032	155.3 ± 7.8	NS
Supine diastolic BP (mm Hg)	100.6 ± 1.9	93.7 ± 2.4	0.012	90.9 ± 2.8	0.002
Standing systolic BP (mm Hg)	161.4 ± 4.2	151.4 ± 5.0	0.006	150.0 ± 10.6	NS
Standing diastolic BP (mm Hg)	106.0 ± 1.9	98.9 ± 2.5	0.005	96.8 ± 2.3	0.002
Standing pulse rate (bpm)	82.6 ± 3.3	75.8 ± 2.2	0.008	63.2 ± 1.7	0.001
Urinary Na output (mEq/24 hr)	113.4 ± 6.2	124.2 ± 8.9	NS	122.6 ± 8.1	NS
Urinary K output (mEq/24 hr)	64.8 ± 5.7	70.1 ± 6.1	NS	65.5 ± 7.5	NS
Serum K (mEq/l)	4.07 ± 0.09	4.41 ± 0.08	<0.001	4.31 ± 0.08	0.008
PRA (ng/ml/hr)	0.90 ± 0.25	0.73 ± 0.26	NS	0.28 ± 0.08	0.006
PAC (ng/100 ml)	11.0 ± 1.2	10.8 ± 1.0	NS	8.8 ± 0.9	0.004
Urinary aldosterone (μg/24 hr)	7.88 ± 0.65	8.10 ± 0.84	NS	6.71 ± 0.48	NS
Hematocrit (%)	44.9 ± 1.3	41.7 ± 1.4	0.002	41.1 ± 1.4	<0.001
Serum creatinine (mg/100 ml)	1.18 ± 0.04	1.19 ± 0.05	NS	1.23 ± 0.05	0.040

BP = blood pressure; PRA = plasma renin activity; PAC = plasma aldosterone concentration; NS = not significant.

*Comparison of pindolol treatment with no treatment.

†Comparison of propranolol treatment with no treatment.

‡ $\bar{x} \pm \text{SE}$.

Traub, Y. M., M. Rabinov, et al. (1980). "Elevation of serum potassium during beta blockade: Absence of relationship to the renin-aldosterone system." *Clin Pharmacol Ther* 28: 765-768.

Beta-blockers: Fall from grace?

Table 2

Strength of Evidence for the Use of Beta-Blockers In Cardiovascular Disease

Conditions	Weak to None	Some Evidence	Strong Evidence
Hypertension (uncomplicated)	✓		
Heart failure			✓
Acute coronary syndrome		✓	
Postmyocardial infarction			✓
Stable angina without MI		✓	
Perioperative (noncardiac surgery)		✓	
HOCM		✓	

HOCM = hypertrophic obstructive cardiomyopathy; MI = myocardial infarction.

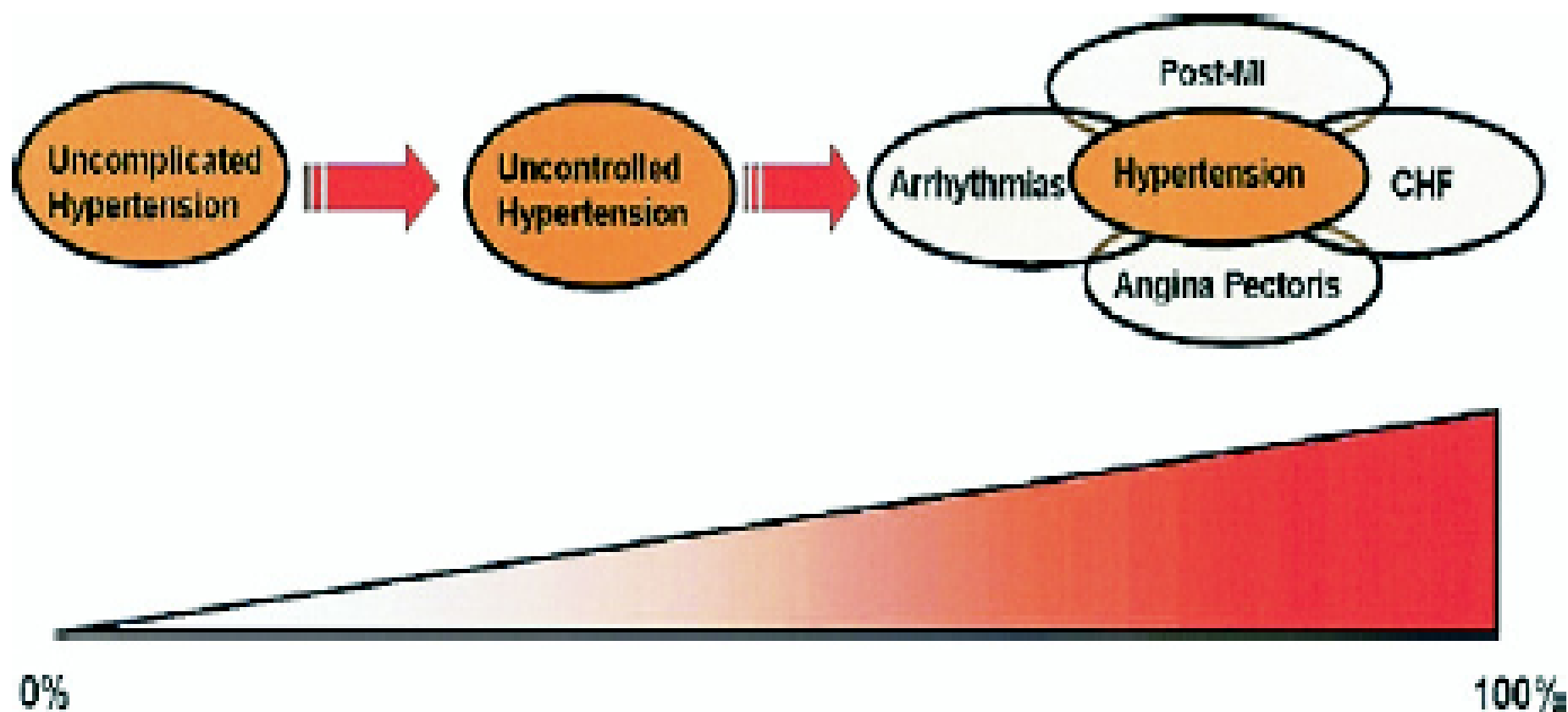


Figure 3

Proposed Use of Beta-Blockers for Hypertension

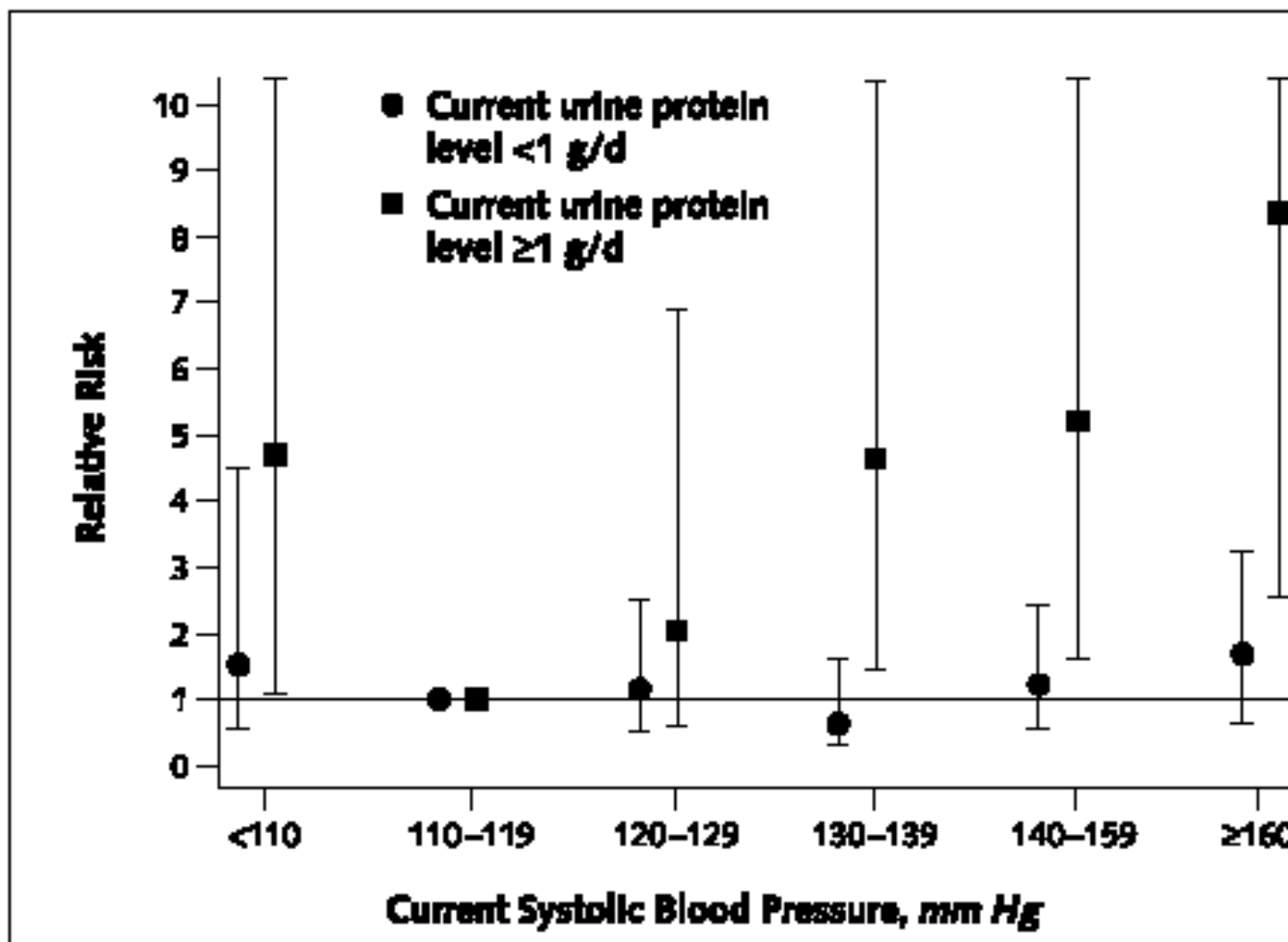
Beta blockers: Fall from grace?

- **Caveat:** “All outcomes studies showing no benefit in HTN were conducted with traditional BBs such as atenolol and metoprolol. Whether the newer vasodilating agents such as nebivolol or carvedilol, which have a more favorable hemodynamic and metabolic profile, will be more efficacious in reducing morbidity and mortality, remains to be determined.” (Bangalore 2007)

Proteinuria: Why should we care?

- **Prognostic:** Higher levels of proteinuria are associated with faster progression of kidney disease and an increased risk of CVD.
- **Toxic?:** The more that protein excretion could be reduced, the better the renal outcomes, down to a level of about 500 mg/day (DeZeeuw 2004)
- Whether proteinuria is a viable surrogate end point is debatable, but many experts recommend a **dual-goal approach** to patients with proteinuric CKD: BP goal and urinary protein goal < 300-500 mg/day (Hirsch 2008 CCJM, DeZeeuw 2004, Schieppati 2003).

Figure. Relative risk for kidney disease progression based on current level of systolic blood pressure and current urine protein excretion.



Jafar, T., P. Stark, et al. (2003). "Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis." *Ann Intern Med* 139: 244-252.

ACEI-ARB combination?

- ACEI-ARB combination therapy reduces proteinuria more than either alone
- Only one trial (COOPERATE) showed its ability to preserve renal function, but methods controversial
- ONTARGET trial showed ACEI-ARB combination did not improve CV outcomes vs. ACEI or ARB monotherapy, and caused more renal dysfunction
 - Caveat: study population did not have proteinuric kidney disease
- For now it remains controversial and is not recommended by many experts
- Instead, maximize dose of ACEI or ARB in an effort to reduce proteinuria (**but far more important to simply treat the HTN!**)

Calcium channel blockers

- Meta-analysis (28 RCTs): non-DHP CCB (verapamil & diltiazem), but not DHP CCB, were associated with a 30% reduction in proteinuria with same magnitude of BP reduction (Bakris 2004)
- In studies with 5-6 years of follow-up, non-DHP CCB preserve kidney function similarly to ACEI (caveat: small, single-center RCTs) (Gashti 2004).
- The addition of non-DHP CCB to an ACEI can lead to further reduction in proteinuria (Bakris 1992 RCT n=30, Bakris 1998 RCT n=37, both used verapamil SR)
- NKF: ***“It would be reasonable to use a combination of a non-DHP CCB and an ACEI or ARB to reduce proteinuria in hypertensive patients.”***

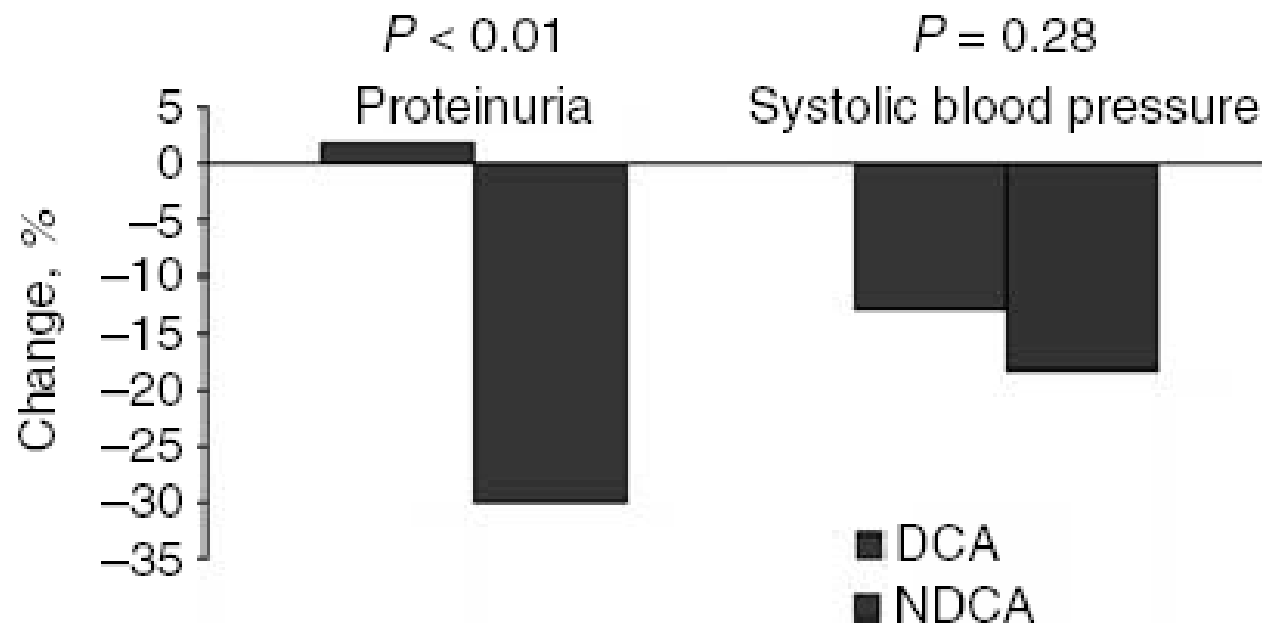


Fig. 1. The change in proteinuria and systolic blood pressure. The percentage change in proteinuria, after adjustment for sample size and study length, for dihydropyridine calcium antagonists (DCAs) and nondihydropyridine calcium antagonists (NDCAs) was 2% and -30%, respectively ($P < 0.01$). The percentage change in systolic blood pressure, after adjustment for sample size and study length, for DCAs and NDCAs was -13% and -18.5%, respectively ($P = 0.28$).

Bakris, G., M. Weir, et al. (2004). "Differential effects of calcium antagonist subclasses on markers of nephropathy progression." *Kidney Int* 65: 1991-2002.

Calcium channel blockers

- Thus, consider using non-DHP CCB over DHP CCB in patients with macroalbuminuria
- The combination of DHP CCB and non-DHP CCB has additive BP-reducing capabilities:
 - Saseen 1996 RCT: SBP reduction of 6 and DBP reduction of 8 as compared with nifedipine alone (caveat: n=16).
 - Kaesemeyer 1994: Baseline: 54% of pts had BP >160/90 on 2+ agents. Combination verapamil + nifedipine → 6% of pts >160/90. (caveat: not randomized, n=50)

Calcium channel blockers

Major Cardiovascular Events with CCBs Versus Other Antihypertensive Drugs

CCB Formulation	Number of Trials	Major Cardiovascular Events ^a No. Events/No. Patients (%)		Relative Risk (95% CI)
		CCBs	Others	
Short acting	7	1,222/9351 (13.1)	1,768/11,691 (15.1)	1.09 (1.00–1.18)
Long acting	5	2,567/31,934 (8.0)	3,546/38,278 (9.3)	1.01 (0.96–1.07)
Nondihydropyridine	4	1,359/25,625 (5.3)	1,365/25,848 (5.3)	1.00 (0.93–1.09)
Dihydropyridine	8	2,430/15,630 (15.5)	3,949/24,121 (16.4)	1.05 (0.99–1.11)

^aMajor cardiovascular events included myocardial infarction, heart failure, stroke, and cardiovascular mortality, except in ALLHAT, where composite coronary heart disease included death from coronary heart disease, nonfatal myocardial infarction, coronary revascularization procedures, and angina requiring hospitalization, and in INVEST, where the primary outcome was cardiovascular mortality.

Composed from Eisenberg MJ, Brox A, Bestawros AN. Calcium channel blockers: an update. *Am J Med* 2004;116:35–43.

Calcium channel blockers

Cardiovascular Profile of Calcium Channel Blockers

	Nifedipine	Amlodipine	Diltiazem	Verapamil
Heart rate	↑	↑/0	↓	↓
Sinoatrial node conduction	0	0	↓↓	↓
Atrioventricular node conduction	0	0	↓	↓
Myocardial contractility	↓/0	↓/0	↓	↓↓
Neurohormonal activation	↑	↑/0	↑	↑
Vascular dilatation	↑↑	↑↑	↑	↑
Coronary flow	↑	↑	↑	↑

↓ = decrease; 0 = no change; ↑ = increase

Kaplan, N. M. (2006). Kaplan's Clinical Hypertension. Philadelphia, PA, Lippincott Williams & Wilkins.

Calcium channel blockers

Relative Frequency of Side Effects of Calcium Channel Blockers

Effect	Verapamil	Diltiazem	Dihydropyridines
<i>Cardiovascular system</i>			
Hypotension	+	+	++
Flush	+	-	++
Headache	+	+	++
Ankle edema	+	+	++
Palpitation	-	-	+
Conduction disturbances	++	+	-
Bradycardia	++	+	-
<i>Gastrointestinal tract</i>			
Nausea	+	+	+
Constipation	++	(+)	-

Kaplan, N. M. (2006). Kaplan's Clinical Hypertension. Philadelphia, PA, Lippincott Williams & Wilkins.

Aldosterone antagonists

- Primary aldosteronism in 20% of patients with difficult-to-control HTN (Calhoun 2006)
- This likely underestimates the role of aldosterone excess in treatment resistance
- Multiple studies show dramatic BP reduction with the addition of low-dose (25-50 mg) **spironolactone** in treatment-resistant patients already taking 3+ drugs.
 - Nishizaka 2003 (n=76): ↓ BP by 25/12
 - Mahmud 2005 (n=69): ↓ BP by 28/13
 - Chapman 2007 (n=1,411): ↓ BP by 22/10
(ASCOT-BPLA trial)

Aldosterone antagonists

- **Spironolactone** also binds to progesterone and androgen receptors, so gynecomastia/breast pain, and sexual side effects are not uncommon
 - Gynecomastia or breast pain:
 - 10% in RALES trial
 - 6% in ASCOT-BPLA trial
 - Hyperkalemia (ASCOT –BPLA trial):
 - 4% had serum K >5.5
 - 2% had serum K >6.0

Aldosterone antagonists

- **Eplerenone** is more specific for the aldosterone receptor than spironolactone
 - **non-formulary** on CCHP
- **Amiloride** , an *indirect* aldosterone antagonist (blocks the epithelial sodium channel, which is upregulated by aldosterone), showed similar BP reductions (Calhoun 2006)
 - On CCHP **formulary**

RAAS blockers

- Consideration of using more than one agent that blocks the renin-angiotensin-aldosterone system (RAAS) (eg, ACEI and aldosterone antagonist) or using high doses of these agents requires that you are able to regularly follow the patient's serum potassium, renal function, and volume status.
- Patients that frequently miss appointments or lab draws are not good candidates.

Other agents: **Hydralazine**

- Dose: 25 bid -> 50 bid -> 100 bid
- Adverse effects
 - Headaches, flushing, and tachycardia
 - due to reflex sympathetic activation
 - may be blunted by concomitant beta-blocker use
 - Drug-induced lupus: sex (F>>M) & dose-dependent (Cameron 1984, n=281)

– 50 mg/day:	0%
– 100 mg/day:	5.4% (0% in men)
– 200 mg/day:	10.4% (19.4% in women vs. 4.9% in men)

Other agents: **Clonidine**

- Dose:
 - **oral** 0.1 bid -> 0.2 bid -> 0.3 bid -> 0.4 bid
 - weekly **transdermal patch** 0.1 -> 0.2 -> 0.3 -> 0.4
- Adverse effects
 - Most common: sedation & dry mouth
 - Rebound HTN in setting of abrupt discontinuation
 - More common/severe with higher doses
 - May be exaggerated if concomitant BB use (unopposed alpha) (Lilja 1982)

Max out or move on?

- It is not necessary to “max out” one drug in the algorithm before moving on to the next. In fact, adding a second agent is more effective at reducing BP than doubling the dose of the first agent and likely reduces the risk of side effects. (Wald 2009, Law 2009)
- The “max out” approach may be preferable for patients with whom adherence and/or cost with multiple pills are concerns.